Guidance for Industry

For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the FDA Form 356h "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use"

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the INTERNET at http://www.fda.gov/cber/guidelines.htm

For questions on the content of this draft document contact Gilliam B. Conley, (301) 827-3543.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
July 1998

DRAFT - Not for Implementation

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[Note: Page numbering may vary for documents distributed electronically.]

PART II – ESTABLISHMENT DESCRIPTION SECTION

Guidance for Industry:*
For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the FDA Form 356h, "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use"

GENERAL INFORMATION

I. BACKGROUND

In the Federal Register of July 8, 1997, the Food and Drug Administration (FDA) announced the availability of revised Form FDA 356h, "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use." [3, 5] This document provides guidance on the completion of this form and the content and format of the Chemistry, Manufacturing and Controls (CMC) section and the Establishment Description section of a License Application for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture.

Not all parts of this document will be applicable to all manufacturers. This document, associated references, and the Division of Blood Applications, Blood and Plasma Branch, CBER, may be consulted when preparing a submission.

II. DEFINITIONS

amendment – *Amendment* is the submission of information to a pending license application or a pending supplement, to revise or modify the application or supplement as originally submitted [21 CFR 600.3(ff)]. Any pending supplement (a BLA supplement which has not received FDA approval) or pending application can have additional information submitted to be included in the review. Each addition of information is an amendment to the application or supplement.

applicant – An *applicant* is any legal person or entity who has submitted an application to manufacture a product subject to licensure under section 351 of the Public Health Service Act. The applicant assumes responsibility for compliance with the applicable product and establishment standards. Also see *manufacturer.*

* This guidance document represents the Agency's current thinking on the content and format of the Chemistry, Manufacturing and Controls and Establishment Description information for human blood and blood components intended for transfusion or for further manufacture. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

authorized official – An *authorized official* is a person or persons appointed by the applicant to correspond with the FDA. Authorized officials can initiate a BLA or a supplement to a BLA, discuss applications and supplements with FDA representatives and provide additional information in support of a BLA.[1]

BLA – Biologics License Application – The single license application proposed to replace both the ELA (Establishment License Application) and the PLA (Product License Application).

BLA number – The BLA number is a permanent tracking number for a particular product. It will be assigned to each product sent to FDA for review. The BLA number will look like: "BL1234."

Manufactures of blood and blood components will receive a single BLA number that will be assigned to the group of generally recognized human-derived products; e.g., Whole Blood, Red Blood Cells, Plasma, Platelets and Cryoprecipitated AHF.

If a licensed applicant wishes to manufacture additional generally recognized products, or to change an already approved manufacturing SOP, the application will be a supplement to the original BLA. FDA will assign a supplement number which expands on the root BLA number. The BLA supplement number will look like: "BL1234.XXX."

Should an applicant develop a novel product, or a novel use for an existing product, it may be assigned a unique BLA number.

broker – A person or entity who arranges the sale or re-sale of blood and blood components, frequently intended for manufacturing use under a short supply agreement. Short supply agreements are between the licensed manufacturer of the final product and the collection facility, not with brokers. If a broker takes custody (stores or manipulates) blood or blood components, the broker must register with the FDA [21 CFR 607].

CBER – Center for Biologics Evaluation and Research, one of FDA's five centers.

CFR – Code of Federal Regulations.

contractor – Any person or entity, not the applicant, who performs part or all of the manufacturing of the licensed product as a service to the applicant. The applicant assures the contractor's compliance with the applicable product and establishment standards. Both the applicant and the contractor may be legally responsible for the work performed by the contractor.

distributor – Selling agent or *distributor* means any person engaged in the unrestricted distribution, other than by sale at retail, of products subject to license [21 CFR 600.3(aa)].

in-process controls – The analytical or process controls used during the various stages of manufacturing and processing. These control procedures are established to monitor the output and to validate the performance of those manufacturing processes that may cause variability in the characteristics of in-process material and the final product.

license number – A *U.S. license number* is issued by CBER to an applicant upon approval of the applicant's first BLA. The U.S. license number, which must appear on the product label, was formerly known as the establishment license number. Those who currently have an approved PLA and ELA will maintain the same license number; no additional application will be necessary.

manufacturer – *Manufacturer* means any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act; "Manufacturer" also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards [21 CFR 600.3(t)].

manufacturing, divided – *Divided manufacturing* is an arrangement in which two or more manufacturers, each registered with FDA in accordance with 21 CFR parts 207 & 607 and licensed to manufacture a specific biological product in its entirety, participate jointly in the manufacture of the product.[4]

manufacturing, shared – *Shared manufacturing* is an arrangement in which two or more manufacturers are licensed for different aspects of the manufacturing of a product. Neither applicant is licensed for all aspects of the manufacturing. Each manufacturer has an approved Biologics License Application for its part of the manufacturing process. Each participant in a shared manufacturing arrangement should be responsible for significant product manufacturing steps which result in the preparation of an identifiable, stabilized intermediate or end product.[4]

short supply – Permits shipment of unlicensed source material from licensed or unlicensed collection facilities to licensed fractionators. The unlicensed collection facility must be registered with FDA [21 CFR 207, 601.22 and 607]. These activities require oversight by the licensed final manufacturer. The licensed manufacturer reports periodically to FDA regarding production specifications and suppliers of the short supply material.

SOP – Standard Operating Procedure(s).

supplement – A *supplement* is a request to the Director, Center for Biologics Evaluation and Research, to approve a change in an approved license application [21 CFR 600.3(gg)]. An applicant who has received FDA approval for an original BLA submission is licensed to produce the product as presented in the application. Future changes which require FDA review and approval [21 CFR 601.12] should be submitted to the FDA as a supplement. Each supplement is assigned a number which uses the BLA number as a root. The number will appear as in the following example: "BL1234/002." Any amendments submitted to a pending supplement should refer to the supplement number.

III. DIRECTIONS FOR COMPLETING FORM FDA 356h

The following instructions are to assist manufacturers of blood and blood components in the completion of the Form FDA 356h. These instructions are not intended for manufacturers of other biological products.

A. When to Use

The Form FDA 356h should be included with each submission to the FDA relating to a Biologics License Application. It is the "cover sheet" which allows proper identification, routing and filing of the attached information.

Submit the form with each

1. Original application submission
2. Supplement to an approved application
3. Amendment to a pending supplement or to a pending application
4. Annual report
5. New or revised labeling
6. Resubmission

B. Submission Recommendations

All submission materials should be sent to CBER as a single package and should include:

1. Original copy of all submission materials.
   Note: If the submission includes changes to materials which have previously been submitted to the FDA, please annotate the changes and reference the previous submission. Any clearly evident method of annotation can be used; e.g., with a highlight marker, bold print, italic print or with brackets in the page margins.

2. One separate duplicate copy of the original submission materials.
   For **annual reports** send two copies.
   a) Clearly mark as "COPY"
   b) If the original has been specially annotated to demarcate the items which have been changed since an earlier submission, the copy should also be marked.

3. When new or revised labels are part of the submission,
   a) Two copies of each label should be included.
   b) One copy of the *Circular of Information* or other labeling which accompanies the product should be included when it is new or revised.
   c) Each label set (original + copy) should be accompanied by a single Form FDA-2567, "Transmittal of Labels and Circulars."
   d) Labels and the Form FDA-2567 should be detached from the original and duplicates mentioned in sections III.B.1 and III.B.2 above.

Note: Labels need not be submitted when a previously approved label or *Circular of Information* is being used without change. Instead, the FDA assigned "Label Review Number" of the previously approved label should be referenced.

C. Electronic Submissions

The following draft guidance documents announced in the *Federal Register* of June 1, 1998, provide information for electronic submissions of regulatory information relating to the development and marketing of biological products. Submissions in electronic format are voluntary.

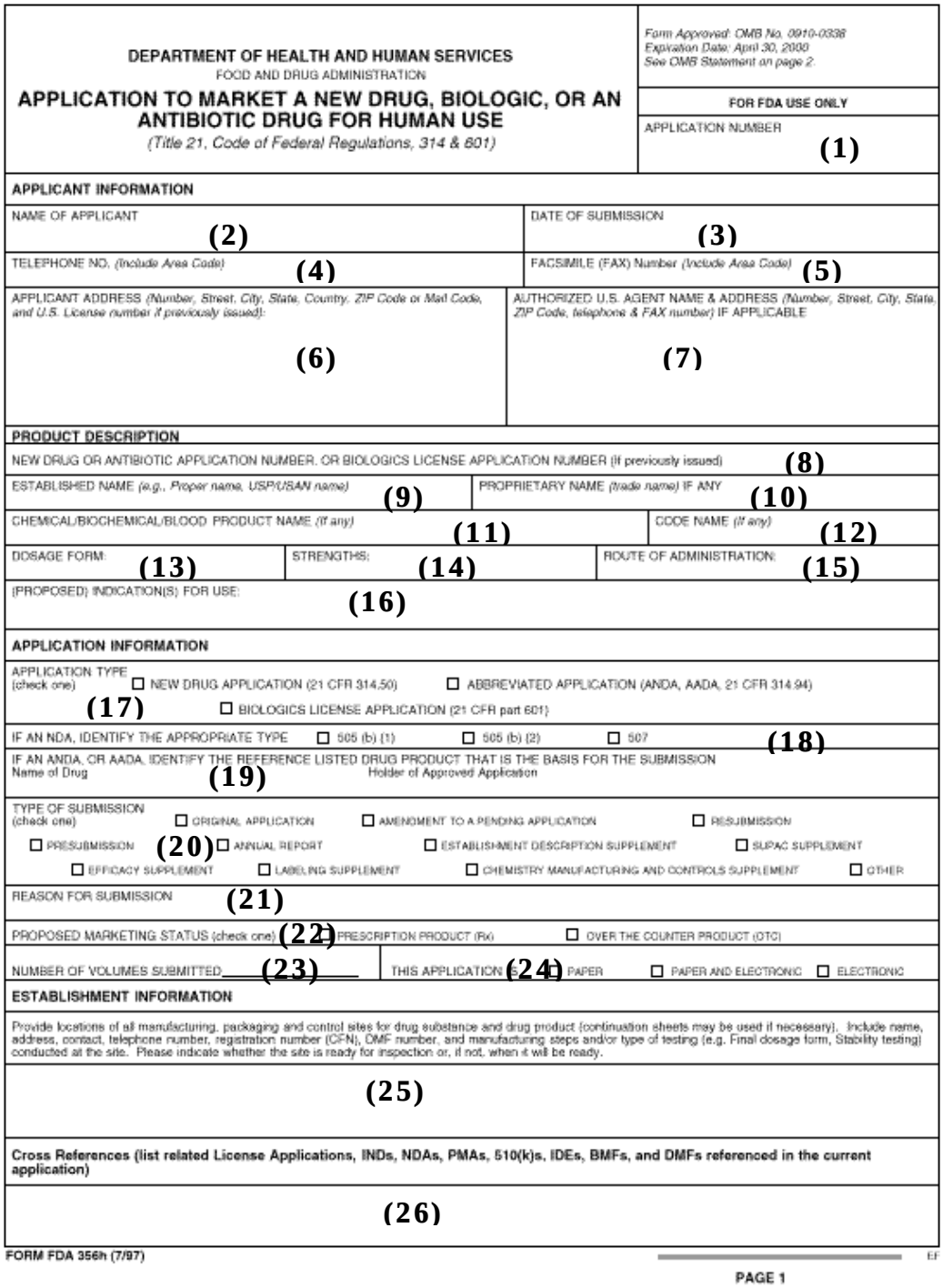
1. Draft "Guidance for Industry: Electronic Submissions of Case Report Forms (CRF's), Case Report Tabulations (CRT's) and Data to the Center for Biologics Evaluation and Research" (63 FR 29739).
2. Draft "Guidance for Industry: Electronic Submissions of a Biologics License Application (BLA) or Product License Application (PLA)/ Establishment License Application (ELA) to the Center for Biologics for Evaluation and Research" (63 FR 29741).
3. Draft "Guidance for Industry: Introductions for Submitting Electronic Lot Release Protocols to the Center for Biologics Evaluation and Research" (63 FR 29742).

D. Detailed Instructions

Any information which will not fit in the allotted space on the form should be included in attached documents.

The information boxes on the front of the Form FDA 356h are numbered in Figure 1 to correspond with the detailed instructions included in this document.

The information boxes on the back of the Form FDA 356h are numbered on the original form. The detailed instructions included in this document are numbered to correspond with the numbering on the form.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER (1)

APPLICANT INFORMATION

NAME OF APPLICANT (2)

DATE OF SUBMISSION (3)

TELEPHONE NO. *(Include Area Code)* (4)

FACSIMILE (FAX) Number *(Include Area Code)* (5)

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: (6)

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE (7)

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) (8)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* (9)

PROPRIETARY NAME *(trade name)* IF ANY (10)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* (11)

CODE NAME *(If any)* (12)

DOSAGE FORM: (13)

STRENGTHS: (14)

ROUTE OF ADMINISTRATION: (15)

(PROPOSED) INDICATION(S) FOR USE: (16)

APPLICATION INFORMATION

APPLICATION TYPE (check one) (17)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507 (18)

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug (19) Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION (20) ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION (21)

PROPOSED MARKETING STATUS (check one) (22) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED (23) THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

(25)

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

(26)

FORM FDA 356h (7/97) EF

PAGE 1

Figure 1: Form FDA 356h (front)

Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use

Front of Form FDA 356h

(1) For FDA use only. Do not write in this block.

(2) The name of the legal entity or person to whom the license will be issued.
- An applicant who is licensed for more than one product should use exactly the same name on all FDA 356h forms submitted.
- The name should be the proper legal name of the corporation or person who is the applicant. A copy of the certificate of incorporation is not necessary.
- Applicant authorized officials should be designated in the establishment description section (item #15 on the back of Form FDA 356h).

(3) The date that the submission materials are completed and forwarded to the FDA.

(4) The phone number(s) of the applicant. Include the country code for foreign manufacturers.

(5) The facsimile number of the applicant. Include the country code for foreign manufacturers.

(6) The applicant's full address (number, street, city, state, zip code) should be listed. Include the country for non-U.S. manufacturers.

Applicants with a previously issued U.S. license number (formerly also known as the establishment license number) should record the number.

(7) If applicable, list the name, full address, phone number and facsimile number for the applicant's authorized U.S. agent. Complete this box only if the applicant is a foreign manufacturer who has authorized a U.S. agent to speak on its behalf on all matters related to FDA licensure and review.

(8) For first time applicants, the BLA number will be assigned at the time of application submission. First time applicants should leave this field blank.

Current holders of approved Establishment License Application (ELA) and Product License Application (PLA) will be assigned their BLA number when the FDA receives the first supplement under the new BLA system. Licensed applicants who have not yet been assigned a BLA number should leave this field blank.

Licensed applicants who have their assigned BLA number should list it here.

If materials are being submitted in support of a pending BLA supplement such as a resubmission in response to a Complete Response Letter, record the BLA supplement number in this field. These materials are amendments to the supplement.

In the rare event that an application is for a novel blood product which has been addressed in another protocol (e.g., IND), list the FDA tracking number for the related submission.

(9) through (10) – Not Applicable – these boxes do not apply to routine blood products. Complete these boxes only if the application is for a novel blood product.

(11) Provide the name of the product or products as it will appear on the product label.

(12) through (15) Not Applicable – these boxes do not apply to routine blood products. Complete these boxes only if the application is for a novel blood product.

(16) For products intended for **transfusion,** the indications for use should be included in the *Circular of Information* submitted with the product labeling. Complete this box only if new indications for use, not previously included in a FDA approved *Circular of Information*, are proposed.

For products intended for **further manufacture,** indicate either "for manufacture into injectable products" or "for manufacture into non-injectable products."

(17) Check the box for Biologics License Application.

(18) and (19) Not Applicable – these boxes do not apply to routine blood products. Complete these boxes only if the application is for a novel blood product.

(20) Blood and blood product applicants should check only one of the following:

- **Original Application** – The inaugural application submitted by the applicant or a new application for a novel product not previously submitted for license. This will only include products for which a new BLA number will be assigned. For manufacturers of blood and blood components, check this box only when submitting an application for a novel blood product or if this will be the first license application for routine blood products.

- **Amendment to a Pending Application** – Additional materials submitted for an application or supplement already under FDA review. Additional materials may be submitted based on further data gathering, such as Quality Control (QC) material, or on FDA written or verbal requests.

- **Resubmission** – Submission of
  - ◊ A complete response to an FDA Complete Response Letter.
  - ◊ An application for a product which was previously withdrawn by the applicant.
  - ◊ An application for a product which previously received a "refusal to file" action from the FDA.

- **Presubmission –** Information submitted prior to the submission of a complete new application, usually in preparation for an applicant/FDA presubmission conference.

- **Annual Report** – Check this box if the form is being used as a cover sheet for the annual report required under 21 CFR 601.12(d).

- **Establishment Description Supplement –** Check if this submission is exclusively to report changes related to the Establishment Description section (item #15 on the back of Form FDA 356h).

- **SUPAC Supplement –** Not Applicable: This option does not apply to blood and blood components.

- **Efficacy Supplement –** Not Applicable: This option does not apply to previously approved blood and blood components. Efficacy information would have to be provided for the first time submission of a novel product.

- **Labeling Supplement –** New or changed labeling for a previously approved product as required under 21 CFR 314.70 and 601.12. (Must also include Form FDA 2567.) This box is checked when labeling is the only reason for the supplement. Labels may also be submitted in support of a current application; check item #2 on the back of Form FDA 356h.

- **Chemistry, Manufacturing and Controls Supplement** – Submission of manufacturing change to an approved BLA. This may include such issues as:
  - ◊ Request to manufacture an additional product covered neither by the original BLA nor by an already approved supplement to the BLA.
  - ◊ Request to manufacture approved products at an additional facility or facilities.
  - ◊ A change to manufacturing protocols being reported as required under 21 CFR 601.12(b) or (c).

- **Other** – Any submission not covered above, such as the submission of data as agreed in post approval commitments. Please note the reason for the submission in the next block.

(21) This section should contain a brief explanation of the reason for the submission, for example "response to Complete Response Letter of 3/10/98" or "revised *Circular of Information* consistent with new CJD Guidance."

If the product is being submitted as a Changes Being Effected (CBE) or a Changes Being Effected in 30 days (CBE-30) supplement under 21 CFR 601.12(c), the required language describing the submission[2] should be noted here and/or at the top of the cover letter.

(22) If the product is intended for transfusion, check "prescription product (Rx)." If the product is for further manufacturing, no box should be checked.

(23) Identify the number of volumes, including and identifying electronic media, contained in the original copy of this submission. Most submissions from blood manufacturers are contained in a single volume. A volume is a bound set of data, such as a notebook. There may be multiple volumes of data in each copy.

(24) CBER is not yet prepared to receive electronic submissions from manufacturers of blood and blood components. Check the box for paper. Blood establishments will be notified when electronic submissions may be used.

(25) Provide the requested information for each facility included in, or affected by, the submission. Include the following information for each facility: name, address, telephone number, registration number (Central File Number), and the name of a contact person. Explain which manufacturing steps or type of testing are performed at each facility. Indicate if each facility is currently prepared for inspection or when it will be ready.

Please note that, when applicable, the complete establishment description is requested under item #15 on the back of Form FDA 356h. That information may be referenced to fulfill the information requirements described here.

For information which is unchanged since an earlier submission, such as a BLA supplement or an Annual Report, reference the earlier submission by date and FDA tracking number.

(26) If the SOP or data related to this application have previously been submitted to FDA, list the FDA tracking number(s) here. This may be a BLA number, a BLA supplement number, or a previous reference number assigned to an ELA or PLA.

- Since blood and blood components will be licensed under a single BLA for each applicant, often there will be no data to be recorded in this box.

- If this application is being submitted for review using a previously approved comparability protocol [21 CFR 601.12(e)], note "COMPARABILITY PROTOCOL" and list the BLA supplement number of the approved protocol.

- If the application is for a novel blood product, list all filings (e.g., BLA, IND, NDA, PMA, 510(k), IDE, BMF, and DMF) referenced in the current application.

Back of Form FDA 356(h)

Items 1 through 19 constitute a check list that should be used to indicate which types of information are included with the submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order of the inclusion of those sections in the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is recommended that, particularly for large submissions, the Index be the first item following the Form FDA 356h.

The CFR references are provided for most items to clarify what information should be submitted in each section. For further information the applicant may consult the guidance information which follows.

Signature – The form is signed and dated by an agent or official authorized by the applicant to represent the applicant to the FDA. The authorized official's typed name, title, address and phone number should be provided in the areas indicated. This is the address and phone number which FDA will use for future contacts regarding this submission. Signature indicates agreement with the "Certification" statement on the form.

PART I – CHEMISTRY, MANUFACTURING AND CONTROLS SECTION

I. PRODUCTS INCLUDED IN "BLOOD & BLOOD COMPONENTS" BLA

The CMC section will include detailed information regarding the manufacture of each licensed product in the applicant's facility or facilities.

The following list of traditional blood and blood component products may be applied for and will be approved under a single BLA. Since variations exist for every product, the approval letter(s) from CBER must be read carefully to determine which product(s) the applicant has been approved to manufacture and distribute. The list may not be all inclusive; that is, additional products may exist or may be developed which will also be approved under a single BLA for blood and blood components.

A. Whole Blood

B. Red Blood Cells

C. Plasma

1. Plasma
2. Fresh Frozen Plasma
   a) From Whole Blood
   b) From automated collection
3. Source Plasma – can be licensed as a stand-alone product, without first being licensed for Plasma.

D. Platelets

1. Single donor Platelets, prepared from Whole Blood
2. Platelets, Pheresis (open and closed systems)

E. Cryoprecipitated AHF

1. Single donor
2. Pooled

F. Source Leukocytes

II. SUPPORTING DOCUMENTATION

All submissions should include appropriate SOP, labels and supplementary information defined in other FDA documents or by current Good Manufacturing Practice (cGMP). See the details below.

Information unchanged from previously approved supplements need not be submitted again. Instead, the information may be referenced by the BLA Supplement identification number. If it contributes to the clarity of the submission, previously submitted information should be included rather than referenced.

A. SOP (Standard Operating Procedure(s))

SOP and all associated forms or information pamphlets, on any of the following topics, should be forwarded to CBER for review and approval:

1. Donor suitability, including donor deferral.
2. Blood collection and processing, including:
   a) Arm preparation;
   b) Sample collection;
   c) Specimen handling; and
   d) List of tests performed, including method used.
   (Do not submit testing SOP, except as noted in product specific information found in other documents.)
3. High risk behavior questions/AIDS information.
4. Donor history forms (including informed consent).
5. Blood and blood component manufacturing for licensed products only:
   a) Submit the SOP for the manufacturing steps in product production; and
   b) Submit the SOP for in-process control testing.
6. Quarantine and disposition of unsuitable product.

Note: Indicate the source of all SOPs included in your submission; e.g., internally developed, obtained from another licensed establishment or from a proprietary organization.

Note: If an SOP change is in response to a Guidance document, follow the instructions in the Guidance document for reporting the change to the FDA.

B. Labeling

Submissions regarding products should include:

1. One Form FDA 2567, "Transmittal of Labels and Circulars," completed and signed by an authorized official.
2. Two copies of each label – may be printer's proofs or final labels.
3. One copy of the *Circular of Information* or other directions for product use, if it is new or revised since the applicant's last approved *Circular.*

Note: If a label has been previously approved and is to be used without change, do not submit for another review. Instead, reference the label review number which identifies the previously approved label.

Note: A standard base label that is used for more than one product may be submitted for review of changes involving an address or viral marker testing on Source Plasma labels. Individual labels should be submitted when new products are collected or manufactured, including the collection of Source Plasma from donors with pre-existing disease associated, RBC or HLA antibodies.

C. Additional Supporting Documentation

In the future, FDA intends to publish additional guidance regarding unique supporting documentation required for specific products and the specific review criteria used by CBER. Until such additional guidance is published, use of the CFR, FDA Memoranda, FDA Guidance, FDA Points to Consider and previously published review checklists[7] should provide sufficient information for the preparation of a complete submission.

III. MANUFACTURING PROCEDURES COMMON TO MULTIPLE TRANSFUSION COMPONENTS

The following processes may be applied to more than one product. For each product included in a submission, the applicant should identify all of the processes used to manufacture the final product. The supporting documentation submitted in the CMC section for each product should include the SOP and labeling as described in Part I, Section II. Additional useful process-specific information to report in the CMC section is described.

A. Irradiation

1. Two months' irradiation logs
2. Dosimetry reports
   a) Annual for Cesium-37
   b) Biannually for Cobalt-60

B. Leukocyte Reduction[9]

1. Include related SOP (e.g., use of sterile connecting device).
2. Identify system used (e.g., filter manufacturer, filter name and model number).
3. Identify when filtration is performed (i.e., during initial 8 hour hold or after units have been refrigerated).
4. Detailed descriptions of all the methods used for in-process controls (e.g., leukocyte counts) including frequency of testing, acceptance criteria and required follow-up when criteria are not met.
5. QC records for at least 2 months (4 units per month or 1% of total monthly production, whichever is greater, for each methodology).

C. Divided Product

1. Include related SOP (e.g., use of sterile connecting device).

D. Washed Product

1. Include related SOP (e.g., use of the sterile connecting device).
2. Identify system used.
3. Provide detailed descriptions of all the methods used for in-process controls (e.g., red blood cell recovery, minimum acceptable level for residual total protein, etc.), including acceptance criteria and required follow-up when criteria are not met.
4. Submit sterility data for ten units of washed Red Blood Cells. If not performed in-house, submit the name and address of the CLIA approved laboratory performing the testing, a copy of the agreement with the outside testing facility, and a statement from the applicant that the sterility testing protocol from the contract laboratory has been reviewed and approved by the applicant.

E. Frozen/Deglycerolized, Rejuvenated, Frozen Rejuvenated, Rejuvenated Deglycerolized

1. Submissions for multiple products may occur sequentially or simultaneously. For example, if an applicant is already approved to produce Red Blood Cells Frozen, the BLA may be supplemented to include frozen rejuvenated Red Blood Cells. Alternatively, if the applicant is not yet licensed for Red Blood Cells Frozen the submission may include data for both products simultaneously. License approval for a product will not be granted until precursory product(s) are approved.
2. Provide detailed descriptions of all the methods used for in-process controls (e.g., glycerol removal, free hemoglobin, Red Blood Cell recovery), including acceptance criteria and required follow-up when criteria are not met.
3. Completed examples of all records and logs used.
4. Sterility data for 10 units of frozen, deglycerolized and/or rejuvenated blood or for 10 lots of Red Blood Cells for immunization. If not performed in-house, submit the name and address of the CLIA approved laboratory performing the testing, a copy of the agreement with the outside testing facility, a letter from the laboratory acknowledging that FDA may inspect the facility and a statement that the sterility testing protocol from

the contract laboratory has been reviewed and approved by the applicant.

IV. MANUFACTURING AGREEMENTS

A. Contractors

Note: The applicant assures all steps performed by the contractor comply with the applicable product and establishment standards for manufacturing or testing performed in support of manufacturing. Both the applicant and the contractor may be legally responsible for the work performed by the contractor.

1. Which contracts to report

Use the following examples as a guide to determine which contracts to report.

a) Do include contractors for services such as:
   (1) Outside testing facilities for tests of record related to the product.
      - Confirmatory testing used for donor re-entry decisions.
      - QC testing such as leukocyte counts, platelet counts and sterility testing.
      - Confirmatory testing used only for donor counseling.
   (2) Outside irradiation facilities.
   (3) Product collection such as apheresis services.
   (4) Off-site storage of blood and blood components.
   (5) Staffing services for personnel directly involved in manufacturing such as donor screening and blood collection.
   (6) Suppliers of RBC for immunization programs.

b) Do not include contractors for services such as:
   (1) Hazardous waste disposal.
   (2) Common carriers and delivery.
   (3) Equipment service and maintenance.
   (4) Housekeeping.
   (5) Donor emergency transport or treatment.

2. List contractor(s)

Provide:

a) A listing of locations and their FDA registration numbers.
b) For any facility not already registered, include a copy of the completed registration, Form FDA 2830. The contractor should send the original form under separate cover to the FDA.

Note: Each facility that collects, manufactures, stores, tests, provides Red Blood Cells for immunization, labels and/or distributes any portion of the manufactured product should be registered with the FDA [21 CFR 607.21 and 607.3(d)]. This may include independent contractors or other company subsidiaries serving as contractors, or other locations/sites owned, operated and contracted by the applicant.

3. Contract summary or summaries

For each contract, summarize the terms of the contract. It is not necessary to include the actual contract. Neither is it necessary to include confidential business information, such as fees and volume discounts. Include:

a) A precise listing and description of the services provided, such as the tests or the manufacturing steps performed.
b) A description of the product or sample shipped to the contract facility.
c) Product or sample shipping requirements to and from the contract facility.
d) A description of the responsibilities of each participant, including the supervision and control exercised by the license applicant, for operations performed at the contract facility.
e) The SOP to be used applicable to the contract arrangement; e.g., procedures used to segregate manufacturing of different products, procedures regarding data transfer and control of data integrity, error reporting agreements and time frames.
f) A description of how and when the contract facility was assessed by the license applicant for compliance with establishment standards and cGMP.
g) The applicant's SOP for periodically assessing the contract facility's compliance with applicable product and establishment standards and cGMP.

4. Explain each contractor's role in the manufacturing process

Through an outline, diagram and/or narrative, explain how the contractors are integrated into the applicant's manufacturing process.

B. Cooperative Manufacturing Agreements – Shared or Divided

1. List participating manufacturers.
2. Provide a detailed description of contractual agreements. Especially specify the particulars of manufacturing responsibilities. Provide at least the information requested in section IV.A.3. above.
3. Through an outline, diagram and/or narrative, explain how these facilities function in the applicant's manufacturing process.

PART II – ESTABLISHMENT DESCRIPTION SECTION

It is FDA's goal to understand the applicant's organizational structure and function well enough to make competent judgments about the ability to produce a quality product in conformance with the law, the regulations and current good manufacturing practices. Contemporary standards for quality manufacturing increasingly focus on issues related to the organization, lines of communication and quality assurance oversight. FDA intends to move toward oversight of manufacturing systems and the applicant's ability to manage those systems in place of the continued review of the details included in SOP, training programs, validation and QC records.

Since it is not FDA's intention to require burdensome reporting, an applicant need not include information regarding the organizational structure in a submission if it has not changed since it was last reported, either in another submission or an annual report. The date and the FDA-assigned tracking number for the document in which the information was last reported should be included in the submission. If it contributes to the clarity of the submission, previously submitted information may be included rather than referenced.

I. ORGANIZATION AND PERSONNEL

A. Organizational Characteristics

Provide a summary of the general characteristics of the organization similar to an annual report of business activities, for example, ownership, principal officers, business partners, not-for-profit status, products (licensed and unlicensed), production volumes, a descriptive summary of the client base, a description of ancillary activities not directly related to blood and blood component manufacturing, etc.

B. Organizational Diagram

Provide an organizational diagram showing reporting authorities, complete with names and descriptive job titles. Include supporting documents as necessary to clarify the organizational structure of the major functional units.

Note: This chart may be included in either a first time BLA submission or in the first annual report for a currently licensed manufacturer. BLA Supplement submissions can refer to the most recent annual report. Send changes in authorized officials to FDA when they occur.

C. Authorized Officials

Provide an up-to-date list of authorized officials[1] – those authorized by the applicant to initiate a BLA or BLA supplement and to discuss licensure and regulatory issues with FDA representatives. The list should include for each authorized official:

1. Name;
2. Title;
3. Mailing address and location (The location is only necessary when the individual's office is different than the mailing address of the applicant.);
4. Phone number (include country code if applicable); and
5. Facsimile number (include country code if applicable).

II. PHYSICAL PLANT AND MAJOR EQUIPMENT

A. Physical Plant

Physical plant information will be reviewed upon inspection for compliance with the CFR [21 CFR 211 & 606] and with cGMP. Records should be filed in an organized fashion in your facility. Do not submit this information with the application.

B. Major Equipment (if applicable to the submission)

In a table, list major equipment used in the manufacture of blood and blood components. Include number of units, model numbers, version numbers, a description of the equipment used and pertinent notes [ex. special chambers used on apheresis equipment].

1. Equipment listed should include, but not necessarily be limited to:
   a) Computer system (central processing unit) and associated software (manufacturer, product name, and version number)
   b) Apheresis equipment;
   c) Blood irradiators;
   d) Sterile connecting devices;
   e) Infectious disease testing instrumentation; and
   f) Self-contained mobile collection units.

2. Equipment which should <u>not</u> be included are:
   a) Computer peripherals such as printers, label printers, terminals;
   b) PC based systems such as word processors and spread sheets;
   c) Laboratory testing equipment other than infectious disease testing instrumentation
   d) General laboratory centrifuges; or
   e) Refrigerators, freezers or other temperature and humidity controlled storage systems.

III. QUALITY ASSURANCE

FDA has described its recommendations for the Quality Assurance (QA) functions in a guidance document.[6] Depending on the size and organization of the applicant's manufacturing operation, the make-up of the staff performing these duties can vary greatly and still successfully accomplish the recommended QA functions. Describe your QA program in detail [21 CFR 211.22(a)]. At a minimum, include information regarding:

A. Reporting Responsibility

Describe who performs the QA functions and how these functions are integrated.
Describe to whom the QA Unit, those performing QA functions, reports.
Describe the QA Unit's position and relationships in the general organizational structure relative to other organizational units.

B. Oversight

Describe the facets of the manufacturing process which are included in the QA Unit's oversight, e.g., internal, contract, materials and supplies, and laboratory testing.

C. Authorities

Describe the issues on which the QA Unit has authority to act.
Describe the issues on which the QA Unit has authority to report.
Describe the issues on which the QA Unit has authority to recommend.

D. Training and Assessment of Personnel

Describe the QA Unit's role in performing or reviewing the training and assessment of personnel in all aspects of the manufacturing process.

E. Competency Evaluation

Describe the QA Unit's activity in performing or reviewing competency evaluations of personnel in all aspects of the manufacturing process.

F. Proficiency Testing

Describe the QA Unit's activity in performing or reviewing proficiency evaluations of personnel in all aspects of the manufacturing process.

G. Systems Validation

Describe the QA Unit's general requirements and/or recommendations for system validation.
Describe how the QA Unit monitors conformance with its validation requirements and/or recommendations.

H. Problem Investigation and Resolution

Describe the QA Unit's system for collecting problem reports.
Describe the QA Unit's approach to problem analysis and trend analysis.
Describe the QA Unit's plan to ascertain the effectiveness of implemented changes and corrections.

I. Audits

Describe the QA Unit's system for designing audits and collecting data.
Describe the QA Unit's approach to analyzing audit data.
Describe the QA Unit's plan to ascertain the effectiveness of implemented changes and corrections.

PART III – REFERENCES

1. Federal Register, 10/15/97, (62 FR 53536), Final Rule: Revision of the Requirements for a Responsible Head for Biological Establishments.

2. Federal Register, 7/24/97, (62 FR 39890), Final Rule: Changes to an Approved Application.

3. Federal Register, 7/8/97, (62 FR 36558), Revised Form FDA 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use; Availability.

4. Federal Register, 11/25/92, (57 FR 55545), FDA's Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biologics.

5. Federal Register, 7/24/97, (62 FR 55545), Guidance for Industry: Changes to an Approved Application: Biological Products; Availability.

6. Federal Register, 7/14/95, (60 FR 36290), Guideline for Quality Assurance in Blood Establishments, Availability.

7. Workshop for Licensing Blood Establishments, 1/30 & 31/95, Sponsored by the FDA, CBER.

8. Memorandum to All Registered Blood and Source Plasma Establishments, "Revision of FDA Memorandum of August 27, 1982: Requirements for Infrequent Plasmapheresis Donors," March 10, 1995.

9. Memorandum to All Registered Blood Establishments, "Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Products," May 29, 1996.

APPENDIX A

FDA Form 356h

Application to Market a New Drug, Biologic,
or an Antibiotic Drug for Human Use

Including standard instructions

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
	( )

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

APPLICANT INFORMATION This section should include the name, street address, telephone and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. Applicant should be entered in the indicated area.

PRODUCT DESCRIPTION This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications the proposed indication should be given. For supplements to an approved application please give the approved indications for use.

APPLICATION INFORMATION If this submission is an ANDA or an AADA, this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

TYPE OF SUBMISSION should be indicated by checking the appropriate box:

Original Application = a complete new application that has never before been submitted;

Amendment to a Pending Application = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

Resubmission = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

Presubmission = information submitted prior to the submission of a complete new application;

Annual Report = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

Establishment Description Supplement = supplements to the information contained in the Establishment Description section (#15) for biological products;

SUPAC Supplement = all supplements submitted under a SUPAC guidance;

Efficacy Supplement = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g. prescription to Over-The-Counter switch;

Labeling Supplement = all label change supplements required under 21 CFR 314.70 and 601.12 that do not qualify as efficacy supplements;

Chemistry, Manufacturing and Controls Supplement = all manufacturing change supplements as required by 21 CFR 314.70, 314.71, 314.72 and 601.12; except SUPAC supplements;

Other = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

REASON FOR SUBMISSION This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request letter of 1/9/97."

NUMBER OF VOLUMES SUBMITTED Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

This application is
☐ Paper ☐ Paper and Electronic ☐ Electronic
Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

ESTABLISHMENT INFORMATION This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

CROSS REFERENCES This section should contain a list of all License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs that are referenced in the current application.

Items 1 through 19 on the reverse side of the form constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follow the Form FDA 356h and, if applicable, the User Fee Cover Sheet (FDA Form 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

Signature The form must be signed and dated by an agent or official authorized by the applicant to represent the applicant to the Agency. The agent's typed name, title, address and phone number should be provided in the areas indicated.